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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,170	12/11/2001	Henry Yue	PF-0733 USN	8478

27904 7590 06/30/2003

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/018,170	YUE ET AL.	
	Examin r	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *205-209,211-217,219-226 and 228-231* is/are pending in the application.

4a) Of the above claim(s) *219-223* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *205-209,211-217,224-226 and 228-231* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

[1] Claims 205-209, 211-217, 219-226, and 228-231 are pending in the application.

[2] Applicant's cancellation of claims 210, 218, and 227 and amendment to claims 205, 213, 215-217, 224-226, and 229-231 in Paper No. 12, filed April 15, 2003, is acknowledged.

[3] Receipt of Declarations under 35 USC 1.132 in Paper Nos. 11 and 13 is acknowledged. It is noted that the Declaration of Paper No. 11 is unsigned and therefore has not been considered. It is further noted that the Declaration of Paper No. 13 appears to be an exact duplicate of the Declaration of Paper No. 11.

[4] Applicant's arguments presented in Paper No. 12 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Lack of Unity

[6] In view of applicant's amendment to limit claims drawn to a polypeptide (claims 205-209) to the polypeptide of SEQ ID NO:12, claims 205-209 are rejoined and have been co-examined with the claims of Group II.

[7] Claims 219-223 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

[8] Claims 205-209, 211-217, 224-226, and 228-231 are being examined on the merits.

Specification/Informalities

[9] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Human Annexin 31 polynucleotide and Polypeptide". See MPEP § 606.01 regarding examiner's change of title.

Claim Objections

[10] Claims 207 and 216 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 101

[11] The rejection of claims 205-209, 211-217, 224-226, and 228-231 under 35 U.S.C. 101 is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 4 of Paper No. 6). Applicants' arguments are summarized and rebutted as follows. For applicant's convenience, the examiner's rebuttal of applicant's arguments will maintain the format as used by applicant in Paper No. 12.

Beginning at page 11 of Paper No. 12, applicant characterizes the invention as a polynucleotide sequence corresponding to a gene that is allegedly expressed reproductive, gastrointestinal, and nervous system tissues and allegedly encodes a polypeptide (SEQ ID NO:12), which has similarities to human annexin 31. Applicant asserts the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which allegedly requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions. Applicant's arguments are not found persuasive. It is noted that, while the claimed nucleic acid is asserted to have been identified from a sample of gall bladder tissue, there is no indication in the specification that this nucleic acid is expressed only in reproductive, gastrointestinal, and nervous system tissues, nor is there indication that this nucleic acid has altered expression in diseased tissues as compared to normal tissues. Absent such a

disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. It is further noted that the determination of tissue expression appears to have been conducted using only a fragment of 45 nucleotides (nucleotides 489-533) of the nucleic acid of SEQ ID NO:64 (see page 91 of the instant specification). Thus, it is possible that nucleic acids other than SEQ ID NO:64 comprising this small fragment have been erroneously identified and expression of SEQ ID NO:64 may or may not occur in reproductive, gastrointestinal, and nervous system tissues. Also, it is unclear as to which specific reproductive, gastrointestinal, and nervous system tissues the alleged expression of SEQ ID NO:64 has been identified, information that would be necessary for a real world use for the claimed nucleic acid.

Beginning at the top of page 12 of Paper No. 12, applicant discusses the Declaration of Dr. Tod Bedilion (hereafter referred to as "Bedilion declaration") of Paper No. 13. Applicant asserts the Bedilion declaration demonstrates the positions and arguments regarding utility of the claimed polynucleotide are without merit. Applicant characterizes the Bedilion declaration as describing some of the allegedly practical uses of the claimed invention in gene and protein expression monitoring applications. In particular, applicant states the Bedilion declaration describes how the claimed polynucleotide can be used in gene expression monitoring systems that were well known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Applicant quotes from the Bedilion declaration, that states (in relevant part) that a cDNA microarray containing a SEQ ID NO:12-encoding polynucleotide would be a more useful tool than a cDNA microarray lacking same in connection with conducting gene expression monitoring studies on proposed (or actual drugs) for treating cancer, immune disorders, neurological disorders, and gastrointestinal disorders for such purposes as evaluating their efficacy and toxicity (page 11, middle of the Bedilion declaration). Applicant's argument is not found persuasive. Initially, it is noted that Dr. Bedilion is a consultant for Incyte Corporation and thus is a concerned party as the Bedilion Declaration states, "I am currently under contract to be a Consultant to Incyte Genomics, Inc." (page 1, middle of the Bedilion declaration). Regarding the merit of the

examiner's position, it is noted that *any* polynucleotide can be used in a microarray, just as any polynucleotide can be used for expression of an encoded protein or as a hybridization probe. Thus, this asserted utility is *not* specific.

At the bottom of page 12 of Paper No. 12, applicant argues the examiner does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring. Applicant argues the examiner's position is the claimed polynucleotide cannot be useful without precise knowledge of its biological function. Applicant argues the law does not require knowledge of biological function to prove utility. Applicant argues it is the claimed invention's use(s) that are subject to analysis of the utility requirement. The examiner agrees with applicants' argument to the extent that the claimed polynucleotide can be used as a probe. As one of ordinary skill in the art would recognize, *any* nucleic acid can be used as a probe – this utility is *not* specific to a particular nucleic acid. The examiner further agrees with applicants' argument to the extent that the utility requirement of 35 USC 101 does not require knowledge of biological function to prove utility. A claimed polynucleotide can meet the legal requirements of utility and enablement as long as the specification discloses a credible, specific and substantial asserted utility or a well-established utility for the claimed polynucleotide. For example, Shattuck-Eidens et al. (US Patent 5,693,473) teach mutant alleles of the *BRCA1* gene that predispose a patient to developing breast and ovarian cancers (abstract). While there is no disclosure of the function of the mutant *BRCA1* genes or their gene products, the invention nevertheless has utility as being an indicator for susceptibility to developing breast and ovarian cancers. Contrary to this example, the instant specification discloses that the claimed polynucleotide encodes a polypeptide that is structurally related to human annexin 31 and predicts that the claimed polynucleotide is involved in various disorders. However, there is no indication that the claimed polynucleotide is differentially expressed or is expressed in an altered form in diseased tissues relative to normal tissues. The specification does not disclose any evidence indicating altered forms or expression levels of the claimed polynucleotide in diseased tissue.

Applicant argues (bottom of page 12 Paper No. 12) that beneficial results can be achieved from the claimed polynucleotide in the absence of any knowledge as to the function of the encoded protein

and assert that the use of the claimed polynucleotide in gene expression monitoring applications are in fact independent of their precise biological function. Applicant's argument is not found persuasive. As stated above, the examiner agrees with applicant's argument to the extent that the utility requirement of 35 USC 101 does not require knowledge of biological function to prove utility. It is evident from the example of Shattuck-Eidens et al. that utility for a polynucleotide does not require knowledge of the encoded polypeptide's function. Applicant's line of argument that all polynucleotides expressed in humans have utility in toxicology testing would appear to support the examiner's argument that the claimed polynucleotide has no *specific* utility. If any polynucleotide expressed in a human has utility in toxicology testing, then that polynucleotide has no *specific* utility as all polynucleotides would have such use. Therefore, any human polynucleotide could be used as a control in toxicology testing and thus this use would not be a *specific* utility. If a specific disease state were correlated with the presence of altered levels or form of a given polynucleotide, then that polynucleotide would have *specific* utility as an indicator of disease. Similarly, all polynucleotides have use for protein expression and the encoded amino acid sequence would be specific and dependent upon the nucleotide sequence of the encoding nucleic acid. However, as all nucleic acids have utility for protein expression, this utility is not specific.

I. The Alleged Applicable Legal Standard

At pages 13-14 of Paper No. 12, applicant cites case law that is allegedly relevant to the instant rejection. The essential disagreement between the examiner's position and that of applicant appears to be the interpretation of what constitutes a specific and substantial utility, as will be explained in detail below.

II. Use of the claimed polynucleotide for diagnosis of conditions or diseases characterized by expression f INTRA, for toxicol gy testing and for drug discovery are allegedly sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph.

Applicant argues the claimed invention meets the necessary requirements for establishing a credible utility under the law as applicants allege there are "well-established" uses for the claimed invention known to persons of ordinary skill in the art and there are allegedly specific practical and beneficial uses disclosed in the specification for the claimed invention. Applicants argue these uses are explained in the Bedilion declaration and that objective evidence, allegedly not considered by the Office, further corroborates the credibility of the asserted utilities. Applicants' arguments are not found persuasive. It is the examiner's position that the claimed invention has no well-established use and there is no specific and substantial use for the claimed invention, even after full consideration of the "evidence" as provided in the specification. Each of these arguments will be described in more detail below.

A. The use of INTRA for toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses that confer "specific benefits" to the public.

Applicant argues (beginning at the bottom of page 14 of Paper No. 12) the claimed invention has real-world utility as allegedly being useful for toxicology testing, drug development, and disease diagnosis through gene expression profiling. Applicant argues these uses are explained in the Bedilion Declaration, the substance of which applicant asserts is not rebutted by the Office action. Applicant argues there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicants asserts that this use is sufficient to establish utility for the claimed polynucleotide. Applicant's arguments are not found persuasive. It is noted that the Bedilion Declaration was not present in the record at the time of drafting the Office action of Paper No. 10 and therefore, was not addressed in said Office action. Regarding the substance of the Bedilion declaration, the examiner agrees with Bedilion to the extent that any polynucleotide, including the claimed polynucleotides, can be included as part of a cDNA microarray, however, this does not confer patentable utility on the claimed polynucleotides as this utility is considered a general use and not a utility that is specific and substantial. MPEP 2107.01 states, "A 'specific utility' is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention". Polynucleotides have a variety of general uses,

such as for hybridization, protein expression, a component of a cDNA microarray – these uses are applicable to *any* polynucleotide and are not specific to the claimed polynucleotide. Also, the claimed polynucleotide has no substantial utility. MPEP 2107.01 states, "Utilities that require or constitute carrying our further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. Contrary to applicant's asserted utility that is not substantial, MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. Similar to applicant's asserted utility, MPEP 2107.01 provides an example of a utility that is *not* substantial: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The claimed polynucleotide has no specific and/or substantial utility, therefore, the use of a cDNA microarray for measuring levels of the claimed polynucleotide is not substantial.

Beginning at the top of page 15 of Paper No. 12, applicant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood this application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. Specifically, applicant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring in connection with developing new drugs for the treatment of cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Applicant's arguments are not found persuasive. The instant specification does not substantiate a link between the claimed polynucleotide and any *specific* disorder associated with cancer, immune disorders, neurological

disorders, and gastrointestinal disorders. The specification merely discloses that the claimed polynucleotide encodes a polypeptide that is structurally related to human annexin 31. MPEP 2107.01 states, "Utilities that require or constitute carrying our further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities". Since the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide, the results of gene expression monitoring assays using a cDNA microarray comprising the claimed polynucleotide would be meaningless without further research. As stated previously, MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. The specification does not disclose any results that would enable a skilled artisan to draw any conclusions regarding a disorder, namely, that the expression of the claimed polynucleotide is expressed at an altered level or form as compared to the corresponding normal tissue. Many genes expressed in diseased tissues have no connection to the disease itself and are not targets for drug development.

At the bottom of page 15 of Paper No. 12, applicant refers to the opinion of Dr. Bedilion who states that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for disorders associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders for purposes of evaluating their efficacy and toxicity. Applicants' arguments are not found persuasive. As previously stated, the instant specification has not established the claimed polynucleotides as being expressed at an altered level or form in a diseased tissue as compared with the corresponding normal tissue. As applicant has provided no evidence that the claimed polynucleotides are involved in the stated disorders, if, e.g., the claimed polynucleotide was a component of a microarray and

a test compound resulted in decreased expression of the claimed polynucleotide, further experimentation would be required to interpret the hybridization results. Disclosure of the claimed polynucleotide as being expressed at an increased level in a specific disorder associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders as compared with the corresponding normal tissue would provide a skilled artisan with an indication that a given test compound that decreased expression of the polynucleotide is a potential candidate drug. However, this disclosure has not been provided and the claimed polynucleotide may very well be expressed at equivalent levels in normal tissues. In the absence of any disclosed relationship between the claimed polynucleotide or the encoded protein and any *specific* disease or disorder, any information obtained from an expression profile would only serve as the basis for further experimentation on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Beginning at the top of page 16, applicant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicant cites Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Applicant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. Applicant's arguments are not found persuasive. While there is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing, the claims are not drawn to this technique. Instead, the claims are directed to polynucleotides that have no specific and substantial asserted utility. As stated above, any polynucleotide can be a component of a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any *specific* disease or disorder based on the teachings of the instant specification would require significant further research. Therefore, this asserted utility is also not substantial.

Beginning at the middle of page 16 of Paper No. 12, applicant asserts the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies than microarrays lacking the claimed polynucleotide. Applicant's argument is not found persuasive. The specification has provided no nexus to link the claimed polynucleotide with any *specific* disease state or disorder. Incorporating the claimed polynucleotide into a microarray would not make the microarray any more valuable than adding any other human polynucleotide. Therefore, the asserted utility is not specific to the claimed polynucleotide.

At the bottom of page 16 of Paper No. 12, applicant argues the examiner does not address the asserted fact that, as described in the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicants conclude that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. Applicant's arguments are not found persuasive. As stated above, *any* polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for *any* polynucleotide. As previously stated, MPEP 2107.01 provides an example of a utility that is *not* substantial as follows: "A method of assaying for or identifying a material that itself has no specific and/or substantial utility". The claimed polynucleotide has no specific and/or substantial utility, therefore, the use of a cDNA microarray comprising the claimed polynucleotide for measuring levels of the claimed polynucleotide is *not* substantial.

At the bottom of page 16 of Paper No. 12, applicant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicants cite case law as allegedly relevant to the patentable utility of research tools. Applicants' arguments are not found persuasive. It is true that a scale, gas chromatograph, screening assays, and nucleotide sequencing

techniques have utility as research tools. However, such tools present a result that requires no further experimentation for interpretation, e.g., a scale provides the mass or weight of an object that requires no further experimentation for interpretation of the result. A more representative analogy to the claimed polynucleotides and array would be that of a scale without a reference of comparison or an identifiable unit of measure - one could place an object on the scale, however, further experimentation would be required to interpret the result and determine the weight of the object. Similarly, as applicants have provided no information regarding altered expression of the claimed polynucleotide, additional experimentation would be required to interpret a result of altered polynucleotide expression obtained using a microarray comprising the claimed polynucleotides. MPEP 2107.01 provides an example of a substantial utility as follows: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use". As stated above, the specification does not disclose a correlation between any *particular* disease or disorder and an altered level or form of the claimed polynucleotide. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or a member of, a microarray is not substantial.

Beginning at the top of page 17 of Paper No. 12, applicant argues there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating disorders associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Applicants argue that, since the specification discloses the claimed polynucleotide to be expressed in reproductive, gastrointestinal, and nervous system tissues and in tissues associated with cancer and inflammation, and expresses a protein that is allegedly known to be associated with diseases such as cancer, immune disorders, neurological disorders, and gastrointestinal disorders, there can be no dispute that an ordinarily skilled artisan could derive more information about relative gene expression than without it. Applicant's arguments are not found persuasive. While the specification of the provisional application (60/139,566) to which the instant application claims domestic priority indicates that the nucleic acid of SEQ ID NO:64 is expressed in gall

bladder tissue (see page 35 of the instant specification), there is no indication that expression of SEQ ID NO:64 is specific for cancer, immune disorders, neurological disorders, and gastrointestinal disorders of reproductive, gastrointestinal, and nervous system tissues. Nor is there indication that this nucleic acid has altered expression in diseased tissues as compared to normal tissue. The specification does *not* disclose the claimed polynucleotide as being expressed at an altered level or form in any particular disease or disorder as compared to the corresponding normal tissue(s). Other than functional assignment of the polypeptide of SEQ ID NO:12 based solely on sequence identity, there is no further indication that the polypeptide of SEQ ID NO:12 is involved in disorders associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Furthermore, even if it can be assumed that the claimed polynucleotides play a role in a disorder associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders, determining which disorder(s) in which tissue(s) is/are involved and how the claimed polynucleotides are altered during the disorder requires significant further research. Absent such a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding normal, i.e., healthy, tissue, further experimentation is necessary for to use the claimed polynucleotide to derive information about a potential drug candidate. Thus, the asserted utility is not substantial.

Beginning at the bottom of page 17 of Paper No. 12, applicant refers to Dr. Bedilion's discussion of the Brown et al. Patent (US Patent 5,807,522; cited by applicant), attached to the Declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. Applicants' arguments are not found persuasive. The claims of the Brown et al. patent are drawn to methods of forming microarrays (see, for example, claim 1 of the Brown et al. patent). Methods of forming a microarray have patentable utility. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale. Furthermore, contrary to a scale, which provides an identifiable unit of weight, a microarray

comprising the claimed polynucleotide would generate a result that requires further research for a real world application. Thus, the asserted utility is not substantial.

At pages 18-19 of Paper No. 12, applicants refer to the references of Rockett et al. (*Xenobiotica* 29:655, cited by applicants) and Lashkari et al. (*Proc Natl Acad Sci USA* 94:8945, cited by applicants) who discuss microarrays and gene expression technology with respect to drug screening and toxicology testing. Applicants' arguments are not found persuasive. Applicants' arguments and alleged supporting evidence merely indicate that microarray technology is important and useful to the scientific community. These publications fail to demonstrate the claimed invention has *any* patentable utility. The use of the claimed uncharacterized polynucleotide in such studies would provide no more information than the use of any other uncharacterized polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide as stated above. Furthermore, due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is allegedly "well-established".

Beginning at the middle of page 19 of Paper No. 12, applicants argue that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Applicants cite the references of Rockett et al. (*Xenobiotica* 29:655), Nuwaysir et al. (*Mol Carcinogen* 24:153), Steiner et al. (*Tox Lett* 112-113:467), Rockett et al. (*Environ Health Perspectives* 107:681), an email from Dr. Cynthia Afshari to an Incyte employee, and examples as set forth at pages 20-21 of Paper No. 12 that allegedly support applicants' assertions. Applicants argue that, because the examiner has allegedly failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and disease diagnosis, the rejections should be withdrawn. Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable.

First, applicants argue that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial, and credible. In this case, all polynucleotides expressed in humans have utility in toxicology testing. However, the specification fails to disclose the methods and information necessary for a skilled artisan to use the claimed polynucleotide for toxicology testing. Therefore, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of proteins or polynucleotides. Thus, such a utility is *not* specific and does *not* constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form and would thus require further research for its implementation. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gleaned from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of proteins or polynucleotides. Even if the expression of applicants' claimed polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information generated using this nucleic acid may have.

With regard to drug discovery and development, applicants mention expression profiling as one use of the claimed polynucleotide. Applicants refer to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, applicants are incorrect in asserting that the efficacy (ability to produce a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological

significance of the polynucleotide(s) which is/are being evaluated. Without this information, the results of the transcript image are useless because one would not inherently recognize how to interpret the result of increased or decreased polynucleotide expression or even what significance could be attributed to such changes in expression profiles. As such information has not been provided in the specification, further experimentation is required to identify a "real world" use for the claimed polynucleotide.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from gall bladder is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed polynucleotide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many polynucleotides are expressed at equal levels and in identical forms in both normal *and* diseased tissues. Therefore, one necessarily needs to know, e.g., that the claimed polynucleotide is either present only in a diseased tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as a diagnostic for disease(s). However, in the absence of any disclosed relationship between the claimed polynucleotides or encoded proteins and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. The similarity of the p lypeptide enc ded by the claimed inventi n t another polypeptide of undisputed utility is asserted to demonstrate utility

Beginning at the middle of page 21 of Paper No. 12 applicants argue that the utility of the claimed polynucleotide can be imputed based on the relationship between INTRA (SEQ ID NO:12 encoded by SEQ ID NO:64) and another polypeptide of unquestioned utility, annexin 31. Applicants argue that the two polypeptides have sufficient sequence similarities to demonstrate a reasonable probability that the utility of INTRA can be imputed to the claimed polynucleotide. Applicant argues it is undisputed that annexin 31 and SEQ ID NO:12 share more than 97% sequence identity. Applicants cite Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) as evidence that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Applicant argues the homology between the polypeptide encoded by SEQ ID NO:64 and annexin 31 is high. Applicant argues that members of the annexin family have been implicated in various diseases. Applicant argues that the phospholipid binding properties of annexins make them "potentially useful" in radionuclide imaging and that this imaging "may be useful" for diagnosing various diseases. Applicant argues the examiner must accept applicants' demonstration that the homology between INTRA and annexin 31 demonstrates utility by a reasonable probability unless evidence or sound scientific reasoning is presented such that a person of ordinary skill in the art would doubt utility. Applicant's argue the references cited by the examiner do not suggest that function cannot be inferred by a reasonable probability. Applicants' arguments are not found persuasive. As far as the asserted "unquestioned" utility of annexin 31, the instant application is not drawn to nucleic acids encoding annexin 31, and, to that extent, the utility of annexin 31 is not at issue. The examiner acknowledges that, based on the relatively high level of sequence identity between annexin 31 and SEQ ID NO:12, it would appear that the function of SEQ ID NO:12 can be inferred from the function of annexin 31 as asserted by applicant. While members of the annexin family may have utility in radionuclide imaging and as a marker of apoptosis as asserted by applicant (page 22, top of Paper No. 12), it is noted that neither the prior art nor the instant specification provides a well-established utility for annexin 31. Instead, the prior art (Morgan et al. *FEBS*

Lett 434:300-304) teaches that, "[t]he biological function(s) and phenotypic profile(s) of annexins remains unresolved" (page 300, left column, top) and provides no indication that annexin 31 is involved in *any* disease, particularly those associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders. Applicant states that the phospholipid binding properties of annexins may be "potentially useful" in radionuclide imaging (page 22, top of Paper No. 12). However, Morgan et al. teach that annexin 31 has "a complete ablation of all four type II calcium-binding sites" (abstract) and that the annexin "[t]ype II calcium-binding sites... ...have been identified as the principal mechanism by which annexins... ...bind phospholipids" (page 300, left column, top). Thus, based on the teachings of Morgan et al., it would appear that, due to the absence of type II calcium-binding sites in annexin 31, neither annexin 31 nor INTRA would be so useful in radionuclide imaging. Furthermore, as annexin 31 and INTRA lack calcium-binding sites responsible for phospholipid binding, neither of these proteins would be so useful for monitoring changes in phospholipid distribution that accompany cell death. Furthermore, Morgan et al. characterize annexin 31 as having an atypical amino acid composition compared to other annexins (page 303, left column, middle), thus indicating that annexin 31 may not function as other annexins. Therefore, even though the polypeptides of annexin 31 and SEQ ID NO:12 may share significant sequence identity, in the absence of a well-established utility for annexin 31, this relationship provides no specific and substantial or well-established utility for the polynucleotide of SEQ ID NO:64.

It is noted that applicants improperly attempt to apply an alleged "rule" of Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078). Brenner et al. (*Proc Natl Acad Sci USA* 95:6073-6078) clearly state that these comparisons "have been assessed **using proteins whose relationships are known reliably from their structures and functions**, as described in the SCOP database" (page 6073, abstract). The art recognizes the proteins within the SCOP database have been *fully characterized* – functionally by empirical laboratory experiments and structurally by generating a three-dimensional structure of the proteins (see for example Murzin et al. *J Mol Biol* 247:536-540). In the instant case, the function of INTRA has not been empirically determined nor has the three-dimensional structure been solved for comparison with annexin 31. Instead, Brenner has expressed his views on functional annotation of a

protein based solely on sequence identity in a manuscript titled "Errors in Genome Annotation" (*Trends Genetics* 15:132-133). In this reference, Brenner (*Trends Genetics* 15:132-133) teaches that laboratory experiments are required to verify a protein's function (page 132, left column, second paragraph) and describes the errors that are inherent in predicting function based on sequence identity. For example, Brenner (*Trends Genetics* 15:132-133) states, "[w]ithout laboratory experiments to verify the computational methods and their expert analysis, it is impossible to know for certain [whether the function assigned to a protein by annotation is correct]" (page 132, left column, second paragraph).

D. Objective evidence is alleged to corroborate the utilities of the claimed invention

Beginning at page 23 of Paper No. 12, applicants argue that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, applicants state that such a showing is conclusive proof of utility. Applicants argue that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest. Applicants state Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Applicants' arguments are not found persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products that lack patentable utility enjoy commercial success, are used, and are considered valuable and applicants' asserted utilities are neither substantial, specific, nor credible. Furthermore, while applicants present evidence showing that the database is commercially valuable, there is no evidence to suggest that the database is any more or less valuable with the inclusion of the claimed polynucleotide.

III. The patent examiner's rejecti ns are allegedly with ut merit.

Beginning at page 24 of Paper No. 12, applicants argue that, rather than responding to the evidence allegedly demonstrating utility, the examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the clamed polynucleotides are not "specific and substantial asserted" utilities. Applicants argue the Office action is incorrect both as a matter of law and as a matter of fact. Applicants' arguments are not found persuasive. The claimed invention has no well-established use and there is no specific, substantial and credible use for the claimed invention, even after full consideration of the "evidence" as provided in the specification. Applicants' arguments will be addressed in more detail as described below.

A. The precise biological role or function of an expressed polynucleotide is allegedly not required to demonstrate utility

Applicants characterize the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Applicants argue that, according to the Office action, it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that applicants are also required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Applicants argue that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Applicants state the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Applicants argue that the present invention meets this test. Applicants argue that the threshold for patentable utility is low and that only throwaway utilities are insufficient, and that knowledge of biological function is not required. Applicants' arguments are not found persuasive. Applicant's arguments have mischaracterized the examiner's position. The examiner has fully considered applicants' "evidence" demonstrating utility and, in accordance with MPEP 2107 and 35 USC 101 has determined the claimed invention to lack patentable utility. Furthermore, the rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility (see item 4 of

Paper No. 6). If a polynucleotide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker and in the toxicology/drug screening microarray assays discussed at length by applicants (see the example of Shattuck-Eidens et al. in US Patent 5,693,473 provided above). However, if a specification does not disclose such information, as is the instant case, then there is no patentable utility. For example, if the claimed polynucleotide were used in a microarray for toxicology testing and if a compound caused the claimed polynucleotide to be expressed at a decreased level in a microarray, what information does this provide, other than to initiate further experimentation. In view of the specification, a skilled artisan would recognize that the determination of whether a compound is potentially therapeutic or deleterious requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray – just as any polynucleotide can be used for protein expression and thus the asserted utility is also not specific.

B. Membership in a class of useful products can be proof of utility

Beginning at page 26 of Paper No. 12, applicants assert the examiner has refused to impute the utility of the members of the annexin family to INTRA. Applicants argue the examiner takes the position that utility of the claimed polynucleotides cannot be imputed unless applicants identify which particular biological function within the class of annexins is possessed by INTRA. Applicants argue the Office would require that all annexins possess a "common" utility in order to demonstrate utility by membership in a class of annexins. Applicants state the case law requires only that the class not contain a substantial number of useless members. Applicants argue the examiner has treated INTRA as if it was in a general class of all polynucleotides, rather than the annexin family. Applicants argue that the examiner has not presented any evidence that the annexin class of proteins has any, let alone a substantial number, of useless members. Applicants argue that annexin family members are phospholipid binding proteins and an ordinarily skilled artisan need not know any more about the claimed invention's function to use it.

Applicant argues the examiner has presented no contrary evidence and knowledge that INTRA is an annexin is more than sufficient to make it useful for diagnosing and treating various diseases. Applicants' arguments are not found persuasive. As stated above, while other members of the annexin family *may* have utility (this statement does not acknowledge the utility of the other annexin family members), the prior art provides no well-established utility for annexin 31. Thus, because applicant asserts SEQ ID NO:12 is related to annexin 31, there would also be no well-established utility for SEQ ID NO:12 or the encoding nucleic acid of SEQ ID NO:64. Instead, Morgan et al. (*FEBS Lett* 434:300-304) clearly characterize annexin 31 as being distinct from other annexin family members. Neither the specification nor the prior art provide evidence that annexin 31 and/or INTRA are involved in *any* disease, particularly those associated with cancer, immune disorders, neurological disorders, and gastrointestinal disorders. As applicant has provided no evidence that the claimed polynucleotides are involved in the stated disorders, further experimentation would be required to determine the relationship of the claimed nucleic acid – if any – to those stated disorders. Furthermore, as annexin 31 has no type II calcium binding sites, annexin 31 would not have the phospholipid binding ability of other annexins. Also, the specification has provided no asserted *specific and substantial* utility for the *entire* class of annexins and there is no well-established utility for this *entire* class of proteins. Therefore, SEQ ID NO:64 would not have utility because of its alleged membership in a class of proteins. Thus the asserted utility is neither specific or substantial.

C. Because the uses of polynucleotides encoding INTRA in toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses beyond mere study of the invention itself, the claimed invention allegedly has substantial utility.

Beginning at page 27 of Paper No. 12, applicants argue the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Applicants state that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. Applicants cite case law allegedly supporting their argument that a material cannot be patentable if it has some other,

additional beneficial use in research. Applicants' arguments are not found persuasive. As discussed above, whereas a scale or gas chromatograph has patentable utility as a research tool as providing a result that can be readily used, in this case, the use of the polynucleotide would require further experimentation as described above. The claimed polynucleotide is not disclosed as having a property (such as a differential pattern of expression in diseased tissue) that can be identifiably and specifically useful without further, additional experimentation. The claimed invention is, in fact, the object of further study, merely inviting further research as evidenced by Morgan et al. (*FEBS Lett* 434:300-304) who teach, "[a]nnexin 31 thus constitutes a unique, natural probe for investigating the role of membrane binding in annexin function" (page 300, abstract). None of the utilities asserted for the claimed polynucleotide meets the three-pronged test of being specific, substantial and credible.

Beginning at the top of page 28 of Paper No. 12, applicants argue the claimed invention has a beneficial use in research for use in toxicology testing, drug discovery, and disease diagnosis. Applicants argue the claimed polynucleotide is a tool not an object of research. Applicants argue the result of gene expression monitoring using the claimed invention is not merely to study the polynucleotide itself, but to study properties of tissues, cells, and potential drug candidates and toxins. Applicants argue that without the claimed invention, information regarding properties of tissues, cells, and potential drug candidates and toxins is less complete. Applicants argue the claimed invention has numerous additional uses as a research tool, including diagnostic assays, chromosomal markers, and ligand screening assays, each of which is allegedly a substantial utility. It is noted that any nucleic acid sequence contained within a chromosome can be used as a chromosomal marker. Furthermore, the specification has provided no *specific* disorder that can be diagnosed using the claimed polynucleotide or treated using a ligand screened by the disclosed method. Thus, the claimed nucleic acid has no specific utility.

IV. By requiring the patent applicant t assert a particular r unique utility, the patent examination utility guidelines and training materials applied by the patent examiner allegedly misstate the law.

Beginning at page 29 of Paper No. 12, applicants challenge the legality of the Patent Examination Utility Guidelines. Applicants are reminded that the examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the examiner has no authority to disregard such guidelines or to apply his own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the Patent Office in accordance with all applicable case law and thus are believed to be consistent therewith. Applicants are further reminded that the examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO. Accordingly, it is the examiner's position that the instant claims, based on an analysis of the utility requirement of 35 USC 101 as set forth in MPEP 2107 and following the current Utility Guidelines, have no specific, substantial, or credible utility.

V. To the extent the rejection of the patented invention under 35 USC 112, first paragraph, is based on the allegedly improper rejection for lack of utility under 35 USC 101, it allegedly must be reversed.

Beginning at page 31 of Paper No. 12, applicants that, to the extent the rejection under 35 USC 112, first paragraph, is based on the improper allegation of lack of utility under 35 USC 101, the rejection fails for the same reasons. Applicant's argument is not found persuasive for the reasons addressing the lack of utility under 35 USC 101 as described above.

Claim Rejections - 35 USC § 112, First and Second Paragraphs

[12] In view of applicant's amendment, the rejection of claims 210, 213-218, and 224-231 under 35 USC 112, second paragraph, as set forth in items 8a-f of Paper No. 10 are withdrawn.

[13] In view of applicant's amendment, the written description and scope of enablement rejections under 35 USC 112, first paragraph, as set forth in items 9 and 10 of Paper No. 10 are withdrawn.

[14] The rejection of claims 205-209, 211-217, 224-226, and 228-231 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated in item 10 above. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102 and 103

[15] In view of applicant's amendment, the rejections of claims 210, 213-215, 217, 218, 224-231 under 35 USC 102 and 103 as set forth in items 11-15 of Paper No. 10 are withdrawn.

Conclusion

[16] Status of claims:

- Claims 205-209, 211-217, 219-226, and 228-231 are pending.
- Claims 219-223 are withdrawn from consideration.
- Claims 205-209, 211-217, 224-226, and 228-231 are finally rejected.
- No claim is in condition for allowance.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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